REMARKS

I. Status of Claims

Prior to this Amendment, claims 1-8, 10, 12, 14-17 were pending in the application, among which claims 2, 14 and 15 are withdrawn and claims 1, 3-8, 10 and 14 - 17 are rejected.

By this amendment Applicants have cancelled claims 2, 3, 10, 12, and 14 - 17. After the entry of this Amendment claims 1, and 4 – 8 are pending in the application.

II. Amendments to the Claims

Claim 1 is amended (a) to limit the disorder to multiple myeloma only and the antibody to 2.13.2, and (b) incorporate the limitations of original claim 3. Thus, claim 1 as amended is drawn to a combination therapy for multiple myeloma, which comprises administering to the patient an effective amount of antibody 2.13.2 in combination with an agent selected from a corticosteroid, anti-emetic, cancer vaccine, analgesic, anti-vascular agent, or anti-proliferative agent. Multiple myeloma is recited in original claims 1 and 16, and antibody 2.13.2 recited in original claims 10 and 12. In addition, claims 4, 6-8 have been amended to more clearly define the term "agent" referred to in each claim. The amendment adds no new matter.

Claims 2, 3, 10, 12, and 14 – 17 have been cancelled by this amendment.

The amendments and cancellation of the claims are for the sole purpose of expediting the allowance of this application. Applicants preserve the right to pursue the cancelled subject matters in one or more continuing applications.

III. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claim 12 is rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite. The basis of the rejection is that the claim depends from cancelled claim 11 thus the method encompassed cannot be ascertained. Applicants have cancelled claim 12, rendering the rejection moot.

IV. Claim Rejections – 35 U.S.C. § 112, First Paragraph

Claim 17 is rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement for treating or preventing aging. Applicants by this amendment have cancelled claim 17, which renders the rejection moot.

V. Claim Rejections – 35 U.S.C. § 103

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Claims 1, 3-8, 10 and 16 stand rejected under 35 U.S.C. § 103, allegedly being obvious over Mitsiades et al. (XP-002293672) in view of Cohen et al. (WO 02/053596) and Masferrer (PGPUB 20040127470) and Carosella et al. (PGPUB 20040209296). Applicants have cancelled claims 3, 10, and 16; therefore, the rejection to them is moot. With respect to the other claims, Applicants respectfully submit that a *prima facie* case of obviousness has not been established for reasons provided in the reply to the previous Office action and for additional reasons detailed below.

Applicants respectfully submit that there is no motivation to modify the reference or to combine the reference teachings to arrive at the claimed invention. As explained above, independent claim 1, as amended, is drawn to a method of treating multiple myeloma, which comprises administering to the patient an effective amount of antibody 2.13.2 in combination with an agent selected from a corticosteroid, anti-emetic, cancer vaccine, analgesic, anti-vascular agent, or anti-proliferative agent. As the Examiner has acknowledged, Mitsaides et al. do not teach a method of administering the anti-IGF-1R antibody 2.13.2 and the combination with various therapeutic agents. The deficiencies of Mitsaides et al. are not cured by Cohen et al., Masferrer, or Carosella et al.

Cohen et al. disclose a large number of antibodies that bind to IGF-1R. Antibody 2.13.2 is only one of the antibodies disclosed by them. Further, Cohen et al. do not mention treating MM with IGF-1R antibodies. In vie w of the disclosure a person skilled in the art would have not reason to select the particular antibody 2.13.2 and combine it with another agent for treating the particular disorder multiple meyloma.

Masferrer et al. relate to a composition that includes a Cox-2 inhibitor and an EGF receptor antagonist, or a method of treating a neoplasia disorder comprising administering a Cox-2 inhibitor in combination with an EGF receptor antagonist. There is simply no teaching about a combination involving an IGF-1R antibody. Further, Masferrer et al. provide an exhaustive list (more than 30 lines long) of specific neoplasia disorders, for the treatment or prevention of which the methods and combinations discussed there may be used, including some rare disorders; however, multiple meyloma, a very common and serious cancer condition, is not included in the list. (See paragraph [0086] on page 5) The exclusion of multiple meyloma from the list teaches

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away from using the method or composition for treating this disorder, rather than motivating a person skilled in the art to combine their teaching with Mitsaides et al.

Carosella et al. relate to a method for selecting solid tumors expressing HLA-G. (See, e.g., the title, Abstract, and paragraph [0001]). It is known in the art that multiple myeloma is not a solid tumor; rather, it is a type of cancerous plasma cells in the blood. Further, there is no teaching in the reference that multiple myeloma expresses HLA-G. Therefore, as with Masferrer et al/, Carosella et al. in fact teach away from the treatment of multiple myeloma. Moreover, absent a motivation to combine the teaching of the references, there can be no reasonable expectation of success in producing the claimed invention.

For at least the above reasons, a *prima facie* case of obviousness can not be established.

Claims 1, 3-8, and 16 also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Mitsiades et al. (XP-002293672) in view of Emanuel et al. (PGPUB 20020151508), Masferrer (PGPUB 20040127470), and Carosella et al. (PGPUB 20040409296). The Examiner noted that the features, upon which Applicants relied, specifically antibody 2.13.2, were not recited in the rejected claims. Applicants have amended claim 1, from which the other pending claims depend, to include the 2.13.2 antibody. Claim 16 has been cancelled; therefore, the rejection to it is moot. With respect other claims, Applicants again submit that a *prima facie* case of obviousness has not been established for the following reasons.

As discussed above, Mitsaides et al. do not teach a method of administering the anti-IGF-1R antibody 2.13.2, nor a combination of this antibody with various therapeutic agents. Also as noted above, both Masferrer and Carosella et al. teach away from treating multiple meyloma. Similarly, Emanuel et al. can not cure the deficiencies of Mitsaides et al. either. Emanuel et al. relate to a method of treating proliferative diseases comprising administering (1) a liposomal anthraxcycline composition in association with (2) an antibody directed against the exctracellular domain of a growth factor receptor and optionally in association with (3) an additional antineoplastic agent. (See, e.g., Abstract). The only growth factor receptor disclosed in Emanuel et al. is erB-2 tyrosine kinase receptor (See, e.g, paragraphs [0004] and [0034]). There is simply no

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disclosure about IGF-1R. Further, Emanuel et al. specifically refer to "methods for treating proliferative diseases, especially breast cancers." (emphasis added). By use of the term "especially" in connection with breast cancers Emanuel et al. clearly teach that the utility of methods referred to there depends on the type of cancers. It is known in the art that breast cancers and multiple meyloma are strikingly different in many aspects, such as physical form (breast caner being solid tumor while multiple meyloma being tumor of blood cells), pathology, etiology, therapies, and so on. In view of the above, a person skilled in the art would not be motivated to combine the teaching of Emanuel et al. and Mitsaides et al. to arrive at the claimed invention for treating multiple meyloma. Further, absent a motivation to combine the teaching of the references, there can no reasonable expectation of success in producing the claimed invention. For at least these reasons, a *prima facie* case of obviousness can not be established.

VI. Concluding Remarks

In view of the amendments and the foregoing remarks, Applicants respectfully request reconsideration of the matter, the withdrawal of all of the rejections, and timely issuance of a Notice of Allowance.

Respectfully submitted,

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